Evaluation and Management of Proteinuria

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Case

- 34 y.o. AD F presents in Germany with headaches, BP of 230/140, Cr=4, and 2 g/day proteinuria. Ultrasound shows bilateral 9.5 cm hyperechoic kidneys.
- Biopsy: focal segmental glomerulosclerosis with extensive fibrous scarring.
- Review of medical records indicates qualitative proteinuria documented several times over previous nine years, never received further assessment.

TAKE HOME MESSAGE

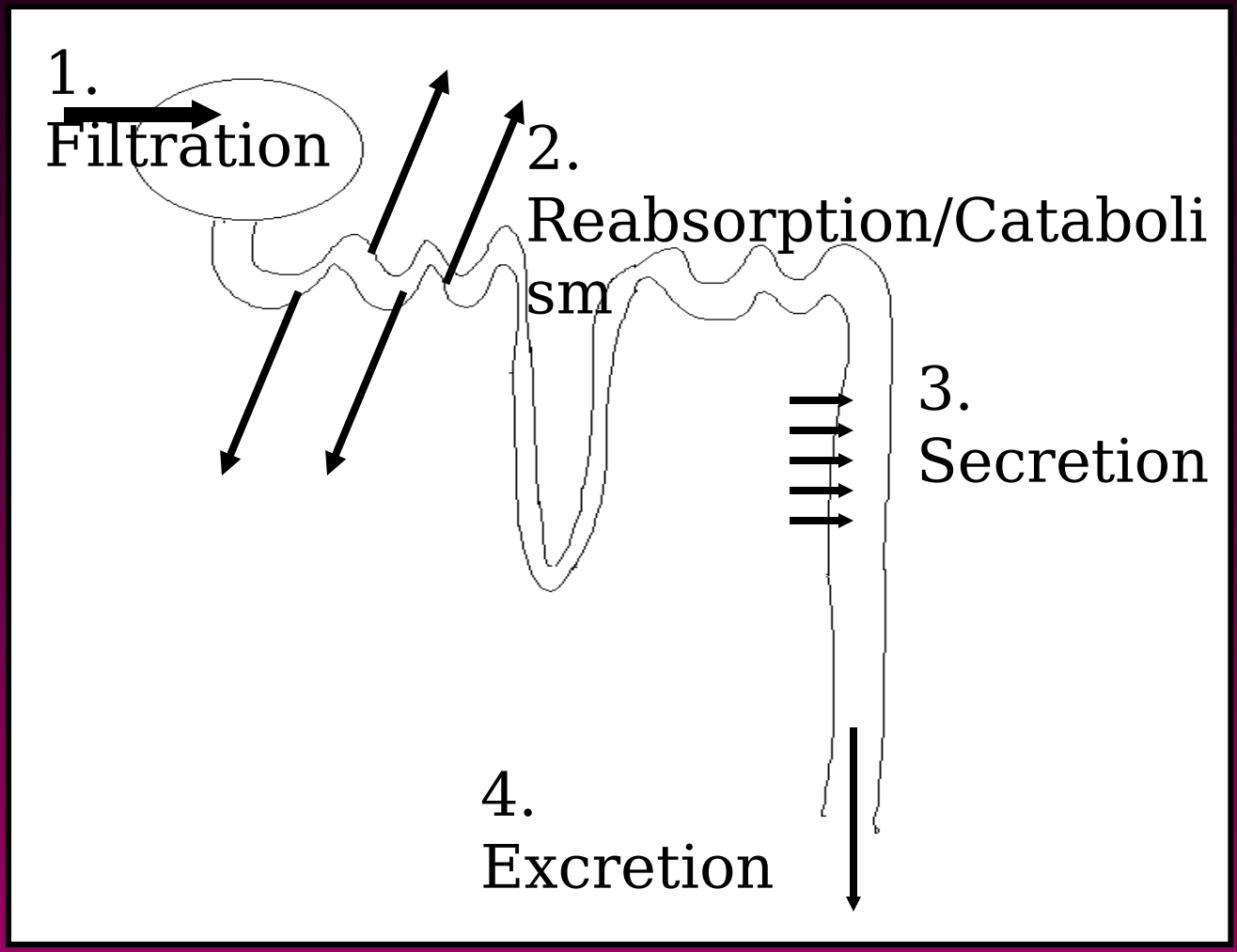
DON'T LET PERSISTENT PROTEINURIA GO UNQUANTIFIED OR UNEVALUATED!

PHYSIOLOGY AND PATHOPHYSIOLOGY OF PROTEIN EXCRETION

Physiology/Pathophysiology

- Protein flow through renal arteries = 121,000 g/day
- Protein filtered through glomerulus = 1-2 g/day (< 0.001%)
- Protein excreted in urine < 150 mg/day (<1% of filtered)
- Composition of normal urine: Tamm-Horsfall protein 60-80%, albumin 10-20%.

Physiology/Pathophysiology Schematic



Physiology and Pathophysiology
Etiologies of Proteinuria

- “Overflow”: excess serum concentrations of protein overwhelm nephron’s ability to reabsorb. Ex.-light chain disease.
- Tubular: deficiency reabsorption of proteins in proximal tubule causing mostly LMW proteinuria. Exs.-interstitial nephritis, Fanconi’s syndrome.
- Glomerular: defect causing albuminuria (>70%) and HMW proteinuria. Exs.-orthostatic proteinuria, glomerulonephritis.

DIFFERENTIAL DIAGNOSIS

Differential Diagnosis
General Categories

- Transient proteinuria
- Orthostatic proteinuria
- Persistent proteinuria

Differential Diagnosis
Transient Proteinuria

- Proteinuria cause by non-renal causes: fever, exercise, CHF, seizures.
- Resolves when condition resolves. No further w/u indicated.
- Intermittent proteinuria: no clear etiology, benign condition with excellent prognosis.

Differential Diagnosis
Orthostatic Proteinuria

- Proteinuria caused by upright position.
- Subjects < age 30 with proteinuria < 1.5 g/day.
- Diagnosis: split day/night urine collections. (Or spot protein/creatinine ratio first AM void and mid afternoon). At WRAMC, there is an order set called "Orthostatic Prot" with a picklist

Differential Diagnosis
Orthostatic Proteinuria

- The most important point is the morning collection, or first AM void spot protein/creatinine ratio, should be NORMAL (extrapolating to <150 mg d over 24 hours, or a ratio of <0.15), not just lower than the afternoon collection.
- Once diagnosis established, excellent long-term prognosis. Annual follow-up recommended.

Differential Diagnosis
Persistent Proteinuria

- Subnephrotic: < 3.5 g/day/1.73 m^2 (usually < 2). Nephrotic: > 3.5 g/day/1.73 m^2.
- Distinction has diagnostic, prognostic, and therapeutic implications but actual value is arbitrary.
- No practical distinction between nephrotic syndrome and nephrotic-range proteinuria.

Differential Diagnosis
Subnephrotic Proteinuria

- Transient or orthostatic proteinuria
- Hypertensive nephrosclerosis
- Ischemic renal disease/renal artery stenosis
- Interstitial nephritis
- All causes of nephrotic-range proteinuria

Differential Diagnosis
Nephrotic Syndrome

- Def: nephrotic-range proteinuria, lipiduria, edema, hypoalbuminemia, hyperlipidemia.
- Implies glomerular origin of proteinuria.
- Clinical manifestations: edema, hypercoagulability, immunosuppression, malnutrition, +/- hypertension, +/- renal failure.

Differential Diagnosis
Nephrotic Syndrome (cont.)

- 75% have primary glomerular disease
- 25% have secondary glomerular disease
  - Medications: NSAIDs, heavy metals, “street” heroin, lithium, penicillamine, α-INF
  - Infections: post-strep, HIV, hepatitis B/C, malaria, schistosomiasis
  - Neoplasms: solid tumors, leukemias, lymphomas, multiple myeloma
  - Systemic diseases: diabetes mellitus, SLE, amyloidosis

Differential Diagnosis
Diabetic Nephropathy

- #1 cause of ESRD in the U.S. (~35% of all ESRD).
- ~ 40% of all diabetics (type I and II) will develop nephropathy.
- Microalbuminuria (> 30 mg/day) develops after ~ 5 years.
  Proteinuria after 11-20 years.
  Progression to ESRD ~15-30 years.

EVALUATION OF THE PATIENT WITH PROTEINURIA

Clinical Evaluation
History

- Onset: acuity, duration
- Diabetic history if applicable, esp. h/o retinopathy/neuropathy
- Renal ROS: edema, HTN, hematuria, foamy urine, renal failure
- Constitutional sxs: fever, nausea, appetite, weight change
- Sxs of coagulopathy: DVT/RVT/P.E.

Clinical Evaluation
History (cont.)

- Rheumatological ROS
- Malignancy ROS
- Medications including OTC and herbals
- Family hx of renal disease
- Exposure to toxins

Clinical Evaluation
Physical Examination

- BP and weight
- Fundoscopic exam
- Cardiopulmonary exam
- Rashes
- Edema

Clinical Evaluation
Labs and Studies

- Required: Chem-16, CBC, U/A, 24-hr urine or spot urine for protein/creatinine
- As clinically indicated: SPEP/UPEP, fasting lipid panel, glycosylated Hg, ANA, C3/C4, urine eosinophils, hepatitis B/C, ophthalmology exam, review of HCM, renal ultrasound +/- Doppler study of veins
- Renal biopsy as indicated

Case

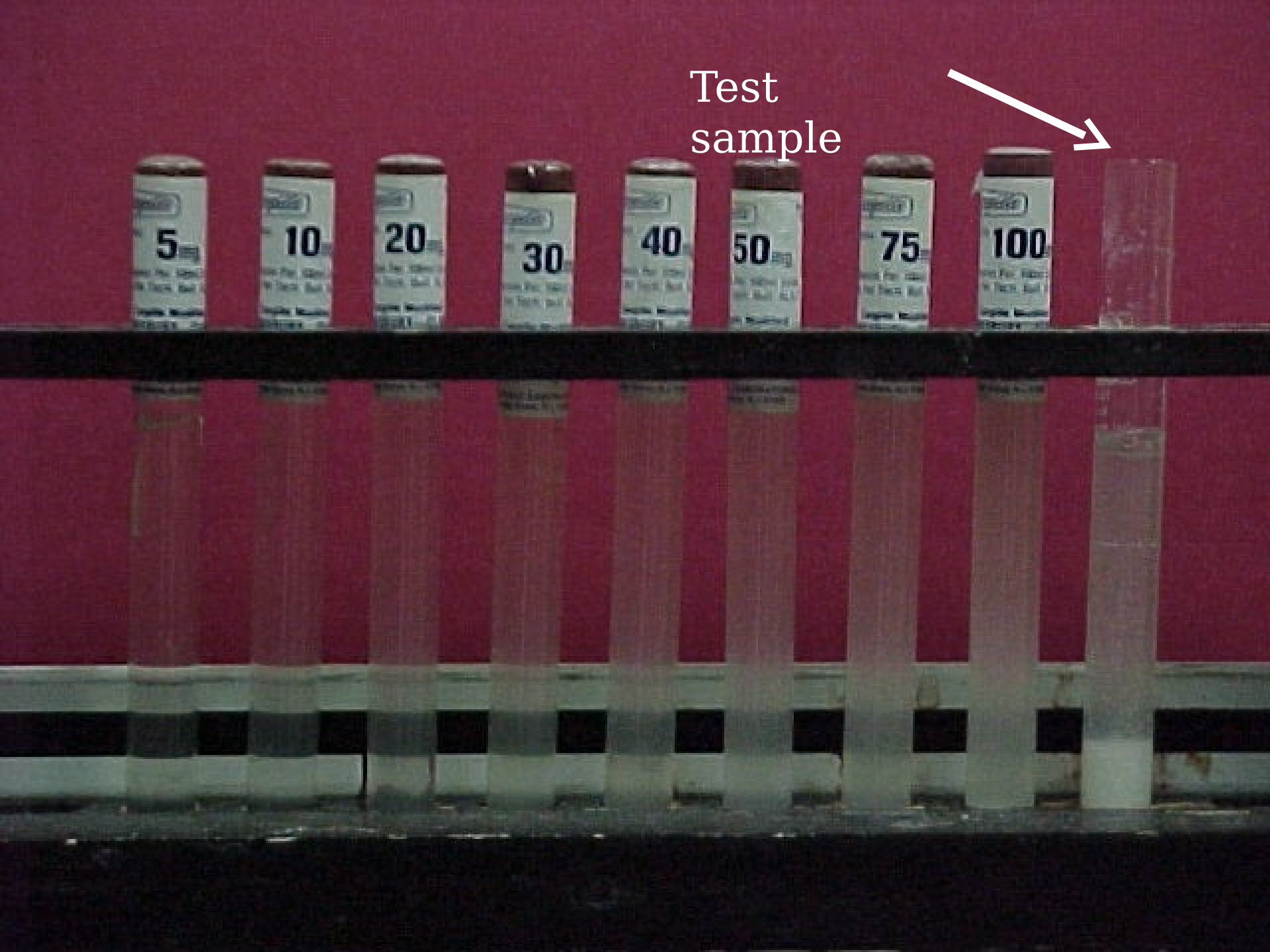
- 35 y.o. AD male presents with massive lower extremity edema and foamy urine. Later notes cough and pleuritic right-sided chest pain, unresponsive to treatment for CAP.
- Labs show 5 g/day proteinuria and normal renal function. Referred to WRAMC.
- Perfusion scan: defect in right lower lobe. Renal CT: renal vein thrombosis on right.

Clinical Evaluation
Urine dipstick

- Most sensitive to albumin, least sensitive to LWM proteins.
- Sensitivity ~ 10 mg/dL (~ 300 mg/day). Coefficient of variability high.
- False negatives: small and positively-charged proteins (light chains), dilute urine.
- False positives: radiocontrast dye, Pyridium, antiseptics, pH > 8.0, gross hematuria.

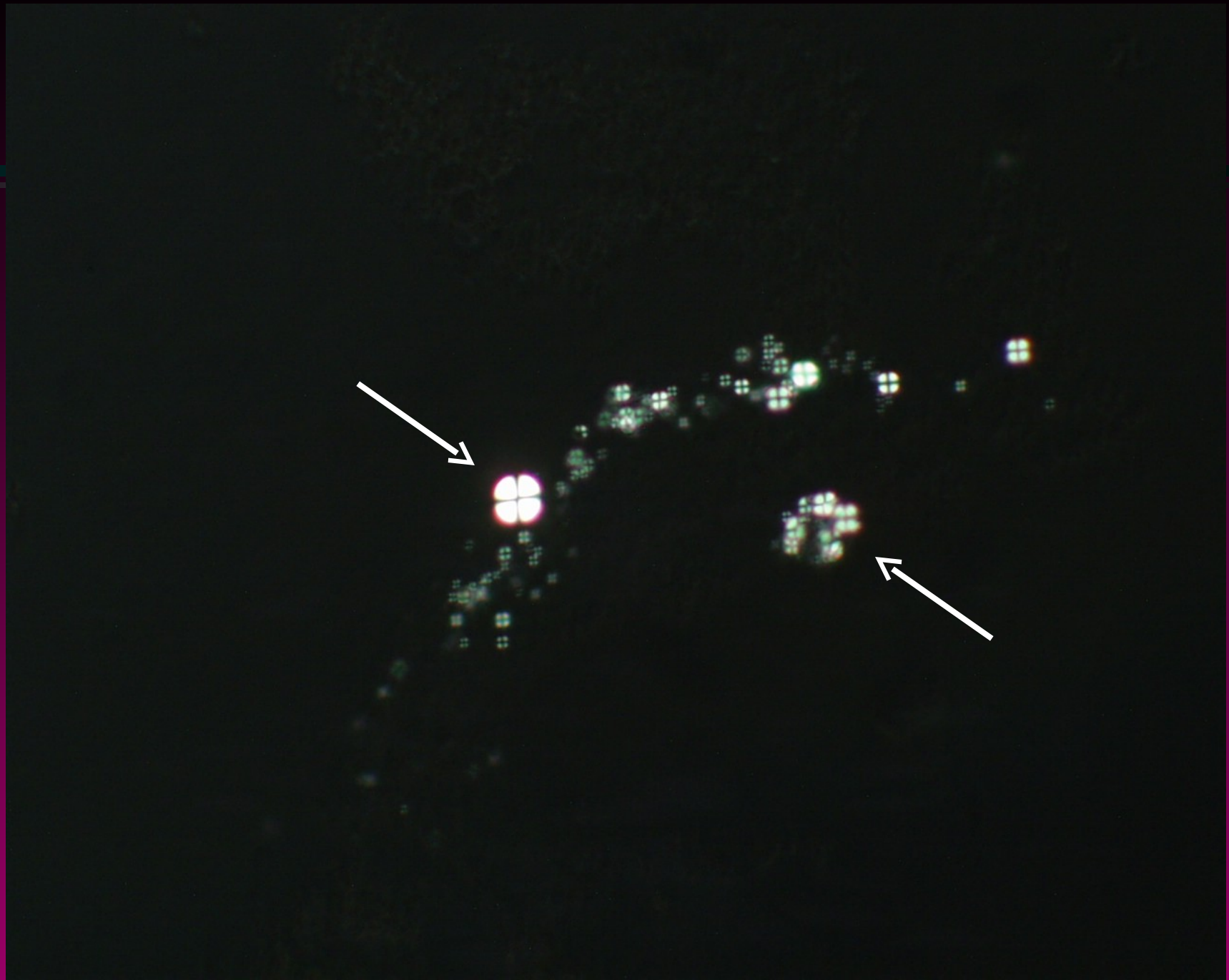
Clinical Evaluation
Sulfosalicylic Acid (SSA) Assay

- Turbidimetric assay based on precipitation of proteins.
- Measures all proteins.


Test
sample
5
10
20
30
40
50
75
100

Clinical Evaluation
Urine Sediment

- Red cell casts or dysmorphic RBCs suggest glomerulonephritis.
- WBCs suggest interstitial nephritis or infection.
- Lipid bodies, oval fat bodies, Maltese crosses suggest hyperlipidemia and possible nephrotic syndrome.



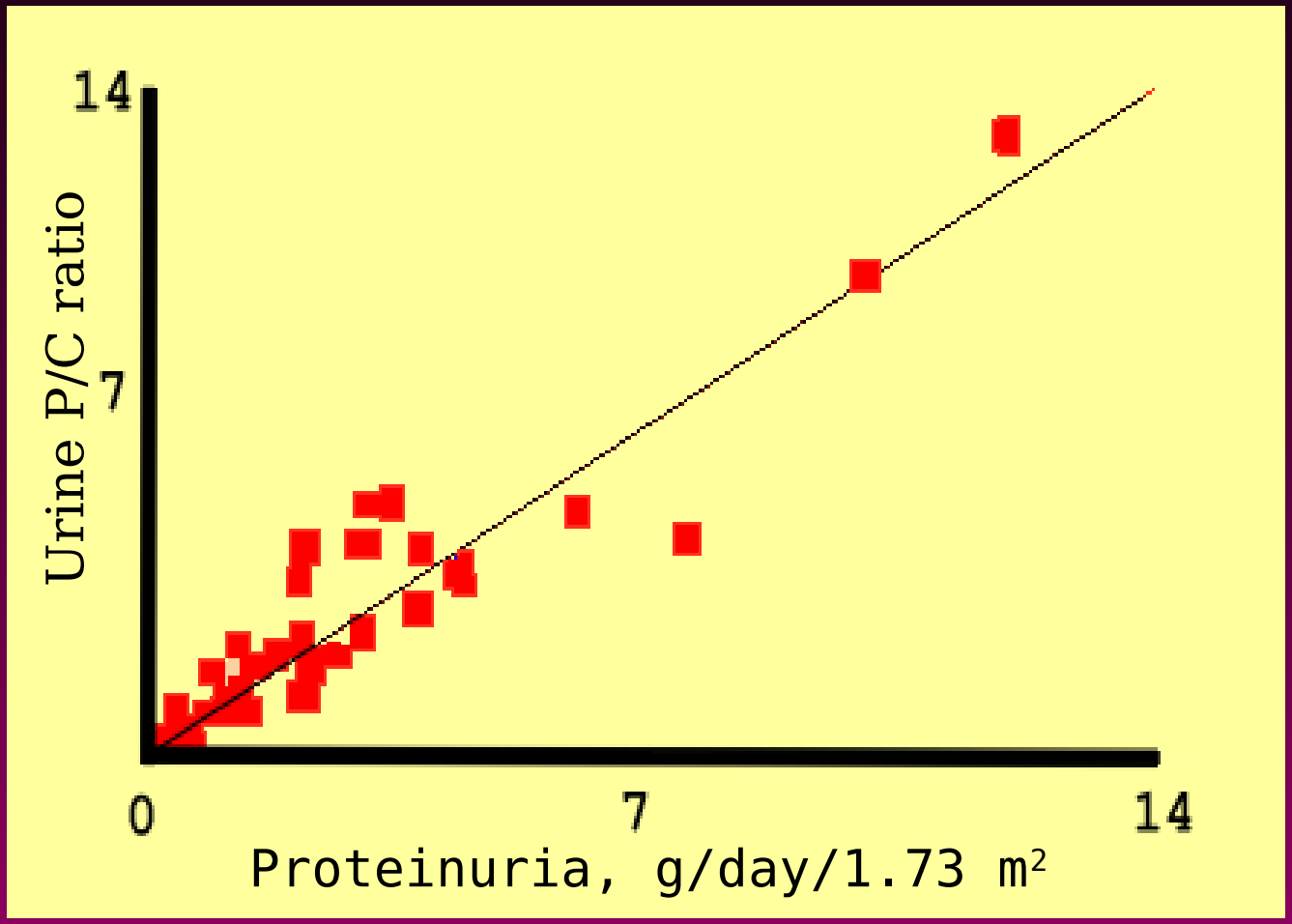
Case

- 67 y.o. WF with trace protein (10 mg/dL) on repeated U/As, SG=1.006, negative blood, glucose, nitrites.
- 24-hr urine collection shows 1.2 g of protein.

Clinical Evaluation
Quantitation of Proteinuria

- 24-hr urine is gold standard, however is often not easily obtained.
- Spot urine protein/creatinine ratio is easier to get, nearly as accurate.
- ALWAYS GET A CREATININE WITH ANY QUANTITATIVE MEASURE OF URINE!
- 24-hr urines: Cr Index = 20-25 mg/kg/day for men, 15-20 mg/kg/day for women.

Clinical Evaluation
Spot Urine Protein/Creatinine Ratio



Adapted from Ginsberg *et al.*, NEJM, 309:1543, 1

Case

- 19 y.o. M presents for Marine induction physical with U/A showing 4+ protein on dipstick, BP = 145/90.
- Spot urine protein/creatinine ratio is 0.02; he is accepted for induction.
- Seven months later he presents with HTN, Cr=13, Hct=20. Renal U/S shows 8.7 and 6.3 cm kidneys. He is started on chronic hemodialysis.

Clinical Evaluation
When to Refer to Nephrology

- Option 1: refer everybody.
- Option 2: refer patients after evaluation for transient and orthostatic proteinuria (unless underlying systemic disease). Diabetics referred at time of microalbuminuria.
- Option 3: never refer. (Let God refer them.)

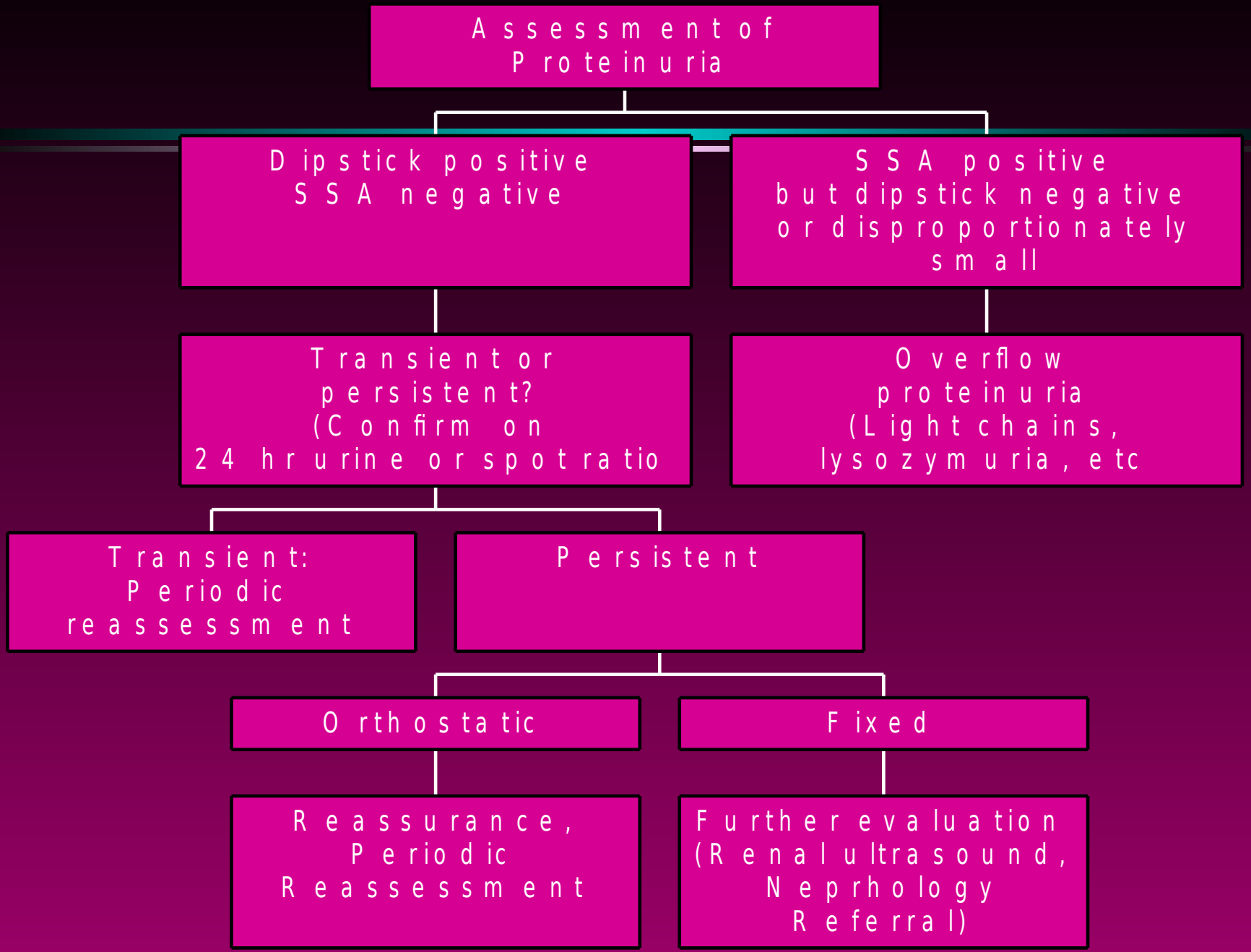
Clinical Evaluation
How to Refer to Nephrology

- Option 1: call or e-mail a nephrologist. (782-6462/6463 or G.Ask A Nephrologist).
- Option 2: send patient with paper consult to nephrology clinic.
- Option 3: schedule through Sierra. (Let God refer them.)

Clinical Evaluation
Who To Biopsy

- Non-diabetic nephrotic syndrome
- SLE for classification
- Planned use of immunosuppressive agents in primary GNs (renal insufficiency, severe edema, hypertension)
- Diagnosis of plasma cell dyscrasias
- < 2 gms proteinuria without other signs: conservative therapy (biopsy resulted in management change in only 3/24 patients in prospective trial)

Evaluation of Proteinuria


Assessment of Proteinuria
Dipstick positive SSA negative
SSA positive but dipstick negative or disproportionately small
Transient or persistent? (Confirm on 24 hr urine or spot ratio
Overflow proteinuria (Light chains, lysozymuria, etc
Transient: Periodic reassessment
Persistent
Orthostatic
Fixed
Reassurance, Periodic Reassessment
Further evaluation (Renal ultrasound, Neprhology Referral)

MANAGEMENT OF PROTEINURIA

Management
Specific vs. Nonspecific Therapies

- Proteinuria is not just a marker of kidney disease, but also a culprit in its progression.
- Control of proteinuria is seen to ameliorate or arrest glomerular disease independent of the underlying etiology.
- Treatment of secondary causes is treatment of the underlying disorder plus supportive care.

Management
Specific vs. Nonspecific Therapies

- Specific therapies on primary glomerulonephritis depending on diagnosis: glycemic control, immunosuppresive agents (corticosteroids, cyclophosphamide, chlorambucil, cyclosporine A, fish oil)
- Nonspecific therapies independent of diagnosis: blood pressure and metabolic control and toward supportive care.

Management
Blood Pressure Control

- Diabetes: control of BP shown to slow progression of nephropathy in several studies.
- Non-diabetics: BP control to MAP < 92 vs. 107 associated with less progression of disease. Benefit greatest in nephrotic patients.
- Gains in stroke and heart disease due to BP control have not been seen in renal disease.

Management
ACE Inhibitors

- Have benefit over and above blood pressure control.
- Type I Diabetes: Captopril use associated with slower progression, less proteinuria without or without co-existing HTN (Lewis *et al*, 1993, Viberti et al, 1994)
- Type II Diabetes: Enalapril use associated with slower progression, less proteinuria. (Ravid *et al*, 1993, 1996).

Management
ACE Inhibitors

- Nondiabetic disease: use of benazepril vs. placebo reduced by 38% the 3-yr progression of renal failure in various diseases. Reduction greater with higher proteinuria (Maschio *et al,* 1996).
- Similar data emerging for angiotensin II receptor antagonists.

Management
Calcium-Channel Blockers

- No benefit with nondihydropyridine agents.
- Diabetes: meta-analysis suggests Non-dihydropyridine blockers may have antiproteinuric effect (Gansevoort *et al,* 1995).
- Would recommend as second-line agent behind ACE inhibitors.

Management
Lipid Control

- Hypoalbuminemia caused increased lipoprotein synthesis by the liver.
- May increase cardiovascular morbidity/mortality.
- Diabetes: small trial suggests that use of lovastatin has beneficial effect on rate of renal progression (Lam *et al.*, 1995).

Management
Glycemic Control

- Type I diabetes: intensive glucose control (HbA1c < 7%) reduced microalbuminuria by 39% and frank albuminuria by 54% (DCCT Study, 1993).
- Type II diabetes: studies underway.

Management
Dietary Protein Restriction

- Experimental data suggests reduced metabolic load slows progression of disease.
- Clinical data is underwhelming (MDRD: no benefit seen except in secondary analysis).
- Probably at most, a small benefit exists.
- Must balance potential benefit of protein restriction with nutritional status.

Management
Supportive Care

- Edema: Cause of significant morbidity. Rx--diuretics, sodium restriction.
- Thromboembolism in nephrotic syndrome: RVT ~35% incidence, other complications ~20% incidence. Prophylactic anticoagulation not recommended.
- Infection: may have low Ig levels, defective cell-mediated immunity. Consider Pneumovax.

PROGNOSIS OF PERSISTENT PROTEINURIA

Prognosis

- Diabetic nephropathy: progression to ESRD over 10-20 years after onset of proteinuria.
- Isolated non-nephrotic proteinuria: 20-yr follow-up shows incidence ~40% renal insufficiency, ~50% HTN.
- Nephrotic syndrome: variable but poorer overall prognosis.

RECOMMENDATIONS

Recommendations
Evaluation

- R/O transient and orthostatic proteinuria.
- Clinical evaluation for systemic diseases, medications, infections, and malignancies as causes of secondary glomerular disease.
- Diabetics: regular screening for microalbuminuria, early use of ACE inhibitors, early referral to nephrology.

Recommendations
Non-specific Treatment

- BP control: < 130/80 for nondiabetics, < 125/75 for diabetics.
- Maximization of ACE inhibitors/AII receptor antagonists and non-dihydropyridine calcium-channel blockers as tolerated.
- Lipid control: TChol < 200, LDL < 100 with HMG Co-A reductase inhibitors.
- Glycemic control for diabetics: A1C < 7%.

Recommendations
Treatment

- Moderate dietary protein restriction: 0.8 mg/kg/day + urine protein losses, careful monitoring of nutritional status.
- Edema: diuretics, sodium restriction
- Specific immunosuppressive therapies for primary glomerular diseases as indicated.